We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Nutrition in Traumatic Brain Injury: Focus on the Immune Modulating Supplements

T.M. Ayodele Adesanya, Rachael C. Sullivan,
Stanislaw P.A. Stawicki and David C. Evans

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/57305>

1. Introduction

The hypermetabolic nature of post-traumatic brain injury (TBI) state makes adequate nutritional support critical. Maintenance of adequate nutritional intake has been shown to have a significant impact on outcomes after TBI. [1] While pre-injury and immediate post-injury malnutrition has been associated with lower survival after TBI, much remains to be learned about the role and optimization of nutritional support beyond the initial phases of recovery. One of the most rapidly evolving aspects of clinical investigation in this general area is focusing on the effects of immune-modulating nutrition on TBI outcomes. The secondary injury phase following brain trauma is characterized by neuroinflammation, free radical generation, excitatory toxicity, and oxidative stress. [2] In this chapter we will present our current state of understanding of immune-nutrition for TBI, highlighting modern clinical practices and emerging trends. Many nutritional supplements have shown promise in preclinical and animal trials, particularly in the area of neuroprotection prior to injury, but human clinical trials have been largely disappointing or nonexistent.

2. General overview of nutritional support following TBI

Trauma, including TBI, is associated with transient immune-suppression and high rates of nosocomial infection. Gastrointestinal mucosal health quickly deteriorates following trauma and stress.[3] Immune-modulating nutrition has been associated with lower complication and infection rates in surgical and critically ill patients and is recommended in SCCM and ASPEN guidelines for select patients including trauma patients. [4] These guidelines make broad

recommendations for the initiation and management of enteral nutrition in critical illness and should serve as the evidence-based foundation for nutritional support programs. Early administration of enteral feeding, combined with immune-modulating nutrient supplementation, has been shown to promote both the structural integrity and immunological function of the gastrointestinal mucosa. Target caloric and protein intake goals should be calculated for each patient, accommodating fully for any baseline increases in nutritional needs due to the metabolic stress of injury. The general initial nutritional strategy should include the provision of more than 50 percent of the estimated total energy expenditure and 1–1.5 g/kg protein within 24 hours of injury. [5] The provision of these requirements by the enteral rather than the parenteral route is always preferred.

3. The immune-enhancing paradigm

Immune-enhancing nutritional ingredients will be the focus of the subsequent sections of this chapter. Specifically, we will discuss the use of omega-3 fatty acids, dietary nucleotides, arginine, glutamine, and various antioxidants in TBI. General principles of the immune-enhancing paradigm focus on aggressive supplementation of immune-modulating ingredients with the aim of promoting healing of injured brain tissue and minimizing loss of parenchyma in the area of penumbra—the threatened but still viable tissue around the periphery of acute brain injury[6]. Many immune-modulating strategies (including steroid administration in CRASH I) have been trialed, frequently without demonstrating benefit[7]. Protocols for the timing, dosage, and route for many of these immune-modulating elements are yet to be clearly defined, and the authors will focus on the most up-to-date evidence regarding the basic science and clinical research on this topic.

4. Omega-3 fatty acids

Omega-3 fatty acids (n-3FAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to be of potential value in the management of patients with TBI. Present in dietary intake, n-3FAs are commonly found in fish oils and are associated with a wide range of possible health benefits. The human brain is composed of 60% lipid by dry weight, with DHA representing one of the most abundant fatty acids found in the brain. [2] N-3FAs contribute to membrane fluidity and thus affect many different aspects of neuronal development and physiology, including cell adhesion, axon guidance, synaptic integrity, and neurotransmission. [2] Additionally, n-3FAs may also play a role in defense against oxidative stress and inflammation.

Biological pathways

N-3FAs have been shown to mitigate the consequences of several key pathologic cellular pathways associated with TBI, including oxidative stress, apoptosis, inflammation, and neuronal excitotoxicity. [2]

- In response to disruption of neuronal membranes, arachidonic acid is released and converted to pro-inflammatory prostaglandins. N-3FA derivatives, on the other hand, inhibit activation and migration of inflammatory cells. Physiologically, n-3FAs also suppress T-cell activation and natural killer cell activity and decrease the total number of circulating leukocytes. [2]
- In the setting of acute oxidative stress, DHA has been demonstrated to lessen the burden of lipid and protein peroxidation. Its metabolites can also modulate expression of tissue repair signals, upregulate anti-apoptotic proteins, and downregulate pro-apoptotic proteins. [8]
- The excitotoxic neurotransmitter glutamate is released following TBI, leading to a disproportionate influx of calcium into neurons and subsequent cell death. [2] *In vitro*, DHA has been shown to decrease calcium influx and thus lessen the burden of glutamate cytotoxicity.

Cumulatively, the effects of n-3FAs on TBI-related cellular processes may promote cell survival and viability, highlighting the potential role of n-3FAs in improving neurological outcomes.

Animal studies

Animal studies investigating the role of n-3FAs in experimental TBI models have produced encouraging results.

- In rat fluid percussion injury (FPI) models, n-3FAs have been shown to decrease oxidative damage as measured by protein oxidation, improve post-traumatic cognitive disability as measured by water maze testing, and normalize dysregulated expression of genes linked to neuronal energy homeostasis. [9, 10]
- In a rat model of controlled cortical impact (CCI), n-3FAs were shown to restore TBI-induced deficits in neuronal dopamine release, important for maintenance of learning, attention, and other neurobehavioral phenomena. [2, 11]
- Finally, in response to impact acceleration TBI in rats, dietary DHA supplementation has been linked to decreased neuronal injury and decreased caspase-3 activity, a marker of apoptosis. [12-14]. Conversely, dietary deficiency of n-3FAs in animal models has been associated with impaired neurogenesis, decreased neuronal size, and neurobehavioral defects. [2] In rat models, n-3FA deficiency has been specifically connected with increased spinal cord vulnerability to neuronal damage, measured by reduced markers of synaptic plasticity and membrane homeostasis in the lumbar spinal cord. [15]

Clinical studies

Despite the laboratory and animal research showing potential benefits of n-3FAs in improving clinical outcomes following TBI, there have been no clinical trials to verify such benefits in human subjects. There have been promising case reports of n-3FA use in TBI and a pilot study which suggested a link between n-3FAs and prevention of post-traumatic psychiatric distress [16, 17], but more robust studies of clinical response will be necessary to ascertain therapeutic benefit. Challenges to conducting effective studies include inconsistent doses and sources of commercially-available n-3FA preparations. Various trials use different doses of n-3FA and the sources are inconsistent as suppliers vary the species of fish used to make fish oils. Low

doses of n-3FA are incorporated in many commercial fish oils but experimental TBI studies typically have focused on higher dose supplementation. [18] Each product also has its own ratio of DHA and EPA. Two prescription n-3FA products are available in the United States, but both primarily consist of EPA.

Clinical Limitations

The clinical use of dietary n-3FAs for TBI has been historically limited by concerns for anti-thrombotic actions, but this concern has subsided with several studies in cardiology patients using combination regimens of fish oil and antiplatelet agents. [19, 20] Other threats to the n-3FA supply, including heavy metal toxicity in some fish oils, also confound the field.

5. Dietary oligonucleotides

Following traumatic brain injury, nucleotides are released into the extracellular space, acting in both an autocrine and paracrine fashion, via nucleotide receptors on neuronal cells. [21] From individual nucleosides to antisense strands and microRNAs, dietary oligonucleotides represent a possible therapeutic means through which the pathophysiological responses and functional outcomes of TBI can be modulated. [22]

Biological pathways

Much work has been done at the single nucleoside level, specifically focusing on the role of adenosine. Adenosine is a purine nucleoside, speculated to play a neuroprotective role in TBI, leading to lower neuronal metabolism and greater cerebral blood flow. [23] Adenosine and its metabolic derivatives have been shown to acutely upregulate after TBI in both animal models and human disease. [24-27] A product of ATP breakdown, cerebral adenosine acts via the purinergic signaling system and may reduce cellular death related to glutamate-mediated excitotoxicity. It also decreases free radical-related/oxidative damage. [28] Although different adenosine receptors have been observed to facilitate both beneficial and deleterious physiologic effects in post-TBI studies, adenosine and its downstream pathways remain clearly linked to the pathophysiology of TBI and represent possible targets for therapeutic modulation. [21, 29-33]

Antisense oligonucleotides, on the other hand, are short synthetic nucleotide strands that can bind to specific messenger RNA (mRNA) targets, making them susceptible to degradation and thus effectively blocking synthesis of corresponding proteins. [34] These nucleotides represent yet another promising avenue through which novel TBI management strategies can begin to utilize more recent biomedical research discoveries.

Animal studies

Animal TBI studies involving oligonucleotide-based therapies have produced some promising results. Oligomeric diets demonstrated potential benefit in rat models of TBI,

preventing TBI-induced weight loss and thymus atrophy and, by extension, averting immune dysfunction. [35]

In terms of specific nucleosides, adenosine is increased in rat fluid percussion injury (FPI) and controlled cortical impact (CCI) models of TBI, and 2-chloroadenosine, an adenosine analogue, has been demonstrated to confer improved bioenergetic and functional outcomes after FPI. [27] Additionally, in a weight-drop closed head injury (CHI) TBI model, intraperitoneal injection of cytidine triphosphate (CTP) has been shown to decrease neuronal apoptosis and improve motor function post-TBI. [36]

Antisense oligonucleotides have also been studied in animal models of TBI.

- In a rat stab wound model of brain injury, antisense oligonucleotides against a monocyte chemoattractant protein (MCP-1) were able to inhibit inflammatory chemokine production. [37]
- In a rat FPI model, pretreatment with antisense oligonucleotides against a specific N-methyl-D-aspartate (NMDA) glutamate receptor (NMDA-R1) decreased mortality from 50% to 8% and improved behavioral recovery, both likely due to the prevention of glutamate excitotoxicity. [38]
- In a murine weight-drop CHI TBI model, injection of oligonucleotides against acetylcholinesterase (AChE) reduced mortality from 50% to 20% in trauma-sensitive mice, decreased post-TBI neuronal death, and improved neuromotor recovery as measured via a beam test for balance and coordination. [34]

Clinical studies

While no clinical studies have explored the use of oligonucleotide-based therapies for TBI, associations have been made in humans between TBI severity and increased CSF concentrations of adenosine. [23, 27] Clinical concerns of oligonucleotide treatments include the cardiovascular effects of purinergic modulation and the effects of oligonucleotides on other unrelated receptor targets. Certainly the array of cell-based and animal studies highlight clear potential for the translational relevance of dietary oligonucleotides. [33, 34]

6. Arginine

Arginine is a nonessential amino acid and is a component of both enteral and parenteral nutrition formulas. [39] Normally, arginine homeostasis is driven by dietary intake and metabolic degradation, and when its utilization increases during growth, development, or injury, arginine may be recognized as an essential amino acid. [39] Parenteral arginine supplementation in trauma patients has been demonstrated to confer improved wound healing and immune responses and has no known adverse effects as a nutritional supplement. [39] From this background, and given that serum levels of L-arginine and its

metabolites have been shown to be significantly reduced in patients post-TBI, arginine represents a potential dietary adjuvant to enhance TBI therapy. [40]

Biological pathways

L-arginine is the immediate, endogenous precursor of nitric oxide (NO), an important physiological vasodilator. [41] Immediately post-TBI, there is an increase of NO, followed by a sustained decrease which can result in diminished cerebral blood flow (CBF) and consequent hypoperfusion. [42] Additionally, arginine is a precursor for proline and 4-hydroxyproline – both important for extracellular matrix (ECM) remodeling – and for creatine – an important energy source in both muscle and brain tissues that will be discussed independently later in this chapter. [40]

Animal studies

Administration of L-arginine has been shown in both rat and mouse controlled cortical impact (CCI) models to restore CBF and reduce contusion volume post-TBI in a dose-dependent manner. [40, 41, 43-48] It has been also been demonstrated in a rat fluid percussion injury (FPI) model to reduce immunoreactivity for nitrotyrosine, a marker of peroxynitrite (ONOO⁻) super oxide radicals. [49, 50] While one study failed to confirm that hypertonic arginine produced significant cerebrovascular improvements over hypertonic saline in a rat FPI model, other dose and time studies in rats have even shown that L-arginine is most neuroprotective when 300mg/kg is given as soon as possible after injury. [39, 51] Rats treated with an arginase-specific inhibitor (N ω -hydroxy-nor-arginine) showed significantly reduced contusion volume post-TBI. [45]

Clinical studies and limitations

There have been no clinical studies exploring the potential therapeutic benefits of isolated arginine supplementation in post-TBI patients. Arginine is a common ingredient in commercially-available formulas and in low doses it appears to be safe. Trials of critical care formulas including arginine, fish oil, and various antioxidants appear to be safe and are effective at reducing infection rates in TBI and other critically-ill patients. [52] Although arginine seems to have strong translational promise, a number of potential risks exist before considering hyper-supplementation of arginine. For instance, while some studies have linked L-arginine to reduced neuronal damage, none have been able to demonstrate the same beneficial effects with regards to neurological function. [43] Secondly, the optimal dose of 300 mg/kg in rats is much larger than amounts of arginine found in typical nutritional formulations. [39] Finally, the roles of other arginine derivatives, such as arginine vasopressin, and nitric oxide (NO) signaling remain unclear in post-TBI pathophysiology. [46, 53-64]

7. Glutamine

Glutamine is a non-essential amino acid, widely distributed throughout the body. It is the most abundant free amino acid in circulation. [65, 66] Glutamine synthesis cannot keep up with

increased requirements such as those experienced during physiological stress, yet it is important for the immune response. Consequently, glutamine supplementation has been shown to decrease infectious complications in trauma patients. [65, 66] The brain serves prominently in glutamine metabolism and is a net producer of the amino acid. [67] In the brain, glutamine is involved in the glutamine-glutamate cycle which functions to conserve the carbon skeletons of neurotransmitters. [67] As part of this cycle, it is synthesized from glutamate and ammonia in astrocytes and also serves as the precursor for glutamate along with alpha-ketoglutarate. [67-69]

While glutamate is recognized as an excitotoxic neurotransmitter released after TBI, patients with brain injury are also observed to experience profound hypoglutaminemia. [67, 68, 70-95] While the cause of this hypoglutaminemia is not known, this observed deficiency provides rationale for dietary supplementation.

Animal studies

While many animal studies assess post-TBI glutamatergic signaling, in a rat TBI model, glutamine administration was shown to decrease concentrations of pro-inflammatory cytokines and apoptotic cells in gastrointestinal tissue, thus reducing TBI-associated damage to gastrointestinal mucosa. [65, 66]

Clinical studies

Limited clinical studies have associated glutamine and alanine dietary supplementation with lower mortality rates, shorter hospital lengths of stay, decreased occurrences of pneumonia and stress ulcers, and higher lymphocyte counts in TBI patients. [96] While these results have been linked to an improved immunological response, future basic science and clinical studies are needed to advance our understanding of the translational potential of glutamine as a nutritional adjuvant in TBI therapy.

As a potential limitation of glutamine therapy, glutaminergic signaling has been implicated in basic science studies with post-traumatic epilepsy. [97] Additionally and perhaps of greater relevance, the recent REDOXS (REducing Deaths due to OXidative Stress) trial sought to investigate the effect of nutritional supplementation in critically-ill patients. A randomized trial, the study found that glutamine supplementation actually resulted in increased harm and mortality in critically ill patients and cautiously advocated that administration of glutamine be reserved for burn and trauma patients not in multiorgan failure. [98] Of note, much of the glutamine in that study was administered in parenteral form, and the body of literature using enteral glutamine has shown no such outcome.

8. Antioxidants

Biologic pathways

Reactive oxygen and nitrogen species (ROS/RNS, respectively) play an integral role in brain injury and posttraumatic neuronal degeneration. [99, 100] In the setting of acute traumatic

stress, endogenous protective mechanisms such as glutathione (GSH) and superoxide dismutase (SOD) may become overwhelmed by increased production of free radicals. [99] This is driven in part by influx of excess of intracellular calcium into mitochondria. Lipid peroxidation mediated by oxygen radical species has been suggested as an important factor in posttraumatic neuronal degeneration. [100] In addition to disrupting the membrane phospholipid architecture, lipid peroxidation contributes to the formation of cytotoxic aldehyde-containing byproducts that bind to and impair the function of cellular proteins. [101] The oxidation of DNA and proteins then may trigger programmed cell death. This process is exacerbated during the reperfusion phase of injury, resulting in additional microvascular damage and neuronal cell death.

Clinical studies

Increasing amounts of evidence point to potential effectiveness of antioxidants in modulating the severity of TBI. [99, 100] Specifically, nutritional antioxidants may be critical in attenuating the deleterious effects of oxidative stress in ischemia and reperfusion type injuries. [102] Specific antioxidant agents that have been investigated in the setting of TBI include vitamin E (alpha-tocopherol), glucocorticoid methylprednisolone, tirilazad mesylate, 21-amino-steroids, green tea extract, ginkgo biloba extract, resveratrol, curcumin, and niacin. [100-102] In addition, evidence points to selenium as being an effective inhibitor of ROS-mediated apoptotic neural precursor cell death in TBI. [103] A full discussion of these antioxidants is beyond the scope of this chapter which focuses on immunonutrition, but several antioxidants are worthy of special mention.

Commercially available enteral formulas frequently tout “added antioxidants,” but these typically are vitamin C, vitamin E, and beta-carotene. In the setting of TBI, enteral nutrition enriched with antioxidants and neuromodulatory agents seems to have some clinical benefit. [104] Although there were no mortality differences between the control and glutamine/probiotic enteral nutrition regimens, the glutamine/probiotic group demonstrated lower infection rates and infections per patient, as well as shorter intensive care stays and fewer ventilator days. [104]

The finding that plasma vitamin C levels are significantly lower in patients with brain trauma suggests that vitamin C plays a potential role in oxidative stress related to brain injury. [105] In addition to vitamin C, other nutritional factors may play a role in modulating oxidative damage associated with TBI, including vitamin E (alpha-tocopherol), beta-carotene, and coenzyme Q10. [106] Despite promising preliminary animal studies, data showing efficacy of specific or combined micronutrient supplementation in the setting of brain injury remains elusive. [106] A small study examining high-dose vitamin C and vitamin E showed some promise but should be interpreted as preliminary. [107]

It has to be noted that phase III clinical trials of neuroprotective agents in TBI have been somewhat disappointing. [108] In a multicenter trial of tirilazad mesylate in TBI, the experimental group was found to have similar mortality and neurologic recovery rates when compared to placebo. [109] However, a subgroup analysis suggested that tirilazad mesylate may contribute to reduced mortality in male patients with severe head injury accompanied by

traumatic subarachnoid hemorrhage (34% tirilazad group mortality versus 43% placebo group mortality). [109]

One trial of polyethylene glycol (PEG)-conjugated SOD in TBI patients initiated within 8 hours of the injury showed a trend toward improved neurological outcomes. [110] Subsequent larger trials failed to reproduce any beneficial effect however. [111] Another agent, U-83836E, a second-generation lazaroid with non-steroidal structure, has been shown to decrease post-injury lipid peroxidation and protein nitration and enhance preservation of mitochondrial respiratory function and calcium buffering ability in a mouse model, and human studies using this agent may be warranted. [112] Melatonin is another antioxidant agent showing promise in providing neuroprotective benefits based on evidence from rat model of TBI. [111] A number of other promising agents have been investigated, but human evidence continues to be scarce.

Increasing amounts of evidence suggests that the most effective antioxidative approach to the brain-injured patient should involve combined treatment with mechanistically synergistic antioxidants. [101] Strategies within such a paradigm should include simultaneous scavenging of lipid peroxidation-initiating free radicals, inhibition of lipid peroxidation propagation, and removal of neurotoxic lipid peroxidation products. [101] Clinical trials with multidrug antioxidant regimens are needed before any recommendations can be made.

9. Branched-chain amino acids

Branched-chain amino acids (BCAAs) are essential amino acids that have important roles in energy metabolism and protein and neurotransmitter synthesis. [113] Valine, isoleucine, and leucine comprise the BCAAs, and these entities have important roles in regulating protein synthesis, gluconeogenesis, and energy metabolism as well as functioning as a major source of nitrogen for producing glutamine in the brain. [113] Because of the important baseline functions of these compounds, this would suggest that alterations in BCAA metabolism after TBI may actually play a role in decreased energy production and neurotransmitter synthesis, thereby contributing to TBI pathology. As such, the supplementation of BCAAs or their metabolites may have a role in the reduction of TBI pathology and possibly outcome.

Biologic Pathways

The metabolism of BCAAs is partially regulated by protein synthesis requirements and excess BCAAs are either catabolized or excreted. In terms of catabolism of excess BCAAs, the first step is catalyzed by the branched-chain aminotransferase isoenzymes, mitochondrial BCATm and cytosolic BCATc. The resulting product of this process is glutamate, which is a major excitatory neurotransmitter as well as a precursor of alpha-ketoglutarate. The second, irreversible step in BCAA catabolism is catalyzed by the mitochondrial branched-chain α -ketoacid dehydrogenase (BCKDC) enzyme complex. [114] BCKDC catalyzes oxidative decarboxylation of the BCKA products of the BCAT reaction, forming NADH and the respective branched-chain acyl CoA derivative of each BCAA. [114]

Animal studies

It is well-established that TBI causes cognitive impairment and altered net synaptic efficacy. In one study where brain injured mice or sham-injured mice either consumed water or water containing BCAAs, there was an overall cognitive improvement with a simultaneous restoration in net synaptic efficacy. [115] The major finding of this study was that dietary delivery of BCAAs ameliorates hippocampal-dependent cognitive dysfunction together with a restoration of net synaptic efficacy after concussive brain injury, and in every animal, cognitive improvement occurred only in conjunction with restored net synaptic efficacy. [115]

Clinical studies

Although the literature on this subject is rather sparse, there are some promising results. It has been reported that the levels of all three BCAAs in patients with mild TBI relative to healthy volunteers is decreased. BCAA levels are further reduced in patients with severe TBI compared with all groups. [113] In one study, it was shown that short-term intravenous supplementation of BCAAs in rehabilitation patients with TBI enhances recovery of cognitive function, induces a supraphysiologic plasma content of BCAAs, and increases tyrosine plasma concentration. [116] This study also revealed that plasma amino acid levels remained decreased in the posttraumatic rehabilitation phase (1-22 months). In this study, 40 patients with TBI were randomly assigned either intravenous BCAAs or placebo. Plasma tyrosine concentration improved in the group given BCAA supplementation and overall disability improvement was greater than that noted in the placebo group. The key conclusion of the study was simply that supplementation of BCAAs in TBI restores plasma levels to the normal range without having a negative effect on levels of precursors of brain catecholamines and serotonin. [116]

Another study revealed that BCAA supplementation may aid in recovery from a posttraumatic vegetative or minimally conscious state, thus reducing the risk of the vegetative state persisting over time. [117] This study, also performed by Aquilani et al., supplemented patients for 15 days by intravenous route with either BCAAs or placebo who were either in a posttraumatic vegetative or minimally conscious states. [117] The 15-day period of these trials is too short to draw any meaningful conclusions regarding that adaptation of BCAAs.

Another study sought to assess the impact of plasma BCAA and tyrosine levels following enterally-administered BCAAs; However, enteral administration failed to return plasma BCAA levels to the normal range. [118] In addition, it was found that elevated plasma phenylalanine was associated with decreased ICP and increased jugular venous oxygen saturation (SjvO₂), while higher plasma isoleucine and leucine levels were associated with increased ICP and higher plasma leucine and valine were linked to decreased SjvO₂. Therefore hyperalimentation with enteral nutrition should be carefully performed to avoid harmful side effects of amino acids while promoting improvements in brain metabolism. [118]

Summary

Although there are a small number of very preliminary but promising studies suggesting that BCAA supplementation may be beneficial to the TBI patient, further studies are needed to

optimize the route and dosage of supplementation and to better elucidate the side effects of artificial supplementation such that supplementation produces no significant side effects.

10. Choline

Immediately following TBI, there is a transient period of excess cholinergic activity which may contribute to excitotoxicity via nicotinic and muscarinic receptor subtypes. However, the chronic phase of TBI is actually associated with decreased brain cholinergic function.

Acetylcholine acts on nicotinic and muscarinic acetylcholine receptors, and previous studies have suggested that TBI-related deficits in α 7 nAChR density may contribute to post-TBI cognitive deficits. [119] If this downregulation of α 7 nACh receptors in fact contributes to the cognitive impairment seen as a result of TBI, a therapeutic option includes drugs or compounds that are selective agonists of α 7 nAChRs and these may be helpful in ameliorating some measures of cognitive decline. [119]

One such compound that has been shown to bind α 7 nAChR is choline. [119] Choline is an essential nutrient available from a wide variety of nutritional sources. It is an important molecule involved in synthesis of structural cell membrane phospholipids, other signaling molecules, and is also a precursor for acetylcholine. [120] As such, it is postulated that dietary choline supplementation may minimize cognitive deficits, reduce brain inflammation, and protect the penumbra.

Biologic pathways

Acetylcholine acts on nicotinic and muscarinic acetylcholine receptors, both of which are prominently located in brain regions that are involved with attention and cognition. [119] As previously stated, choline has been shown to be an agonist at α 7 nAChRs, but not other nicotinic receptor subtypes. α 7 nAChRs are known to be involved in both excitotoxicity and inflammatory pathways. Once TBI occurs, multiple biochemical pathways, including the aforementioned excitotoxicity and inflammatory pathways, are set into motion which leads to a chronic, neurodegenerative condition.

Animal studies

In one study, dietary choline supplementation was shown to significantly reduce brain injury-induced spatial learning deficits in a rat model. Additionally, the choline-supplemented diet helped reduce brain inflammation and spared cortical tissue. [119]

It is known that administration of cytidine-5'-diphosphate (CDP)-choline functions as a neurostimulant in neurological disorders of memory. [121] As such, its use in TBI was promising. Dixon et al. demonstrated that chronic CDP-choline treatment can attenuate neurological and cognitive performance deficits following TBI in rats. [122] CDP-choline treatment also increased post-injury resistance to the memory-disrupting effects of scopolamine. Exogenous administration of CDP-choline increased ACh release. [122] The mechanism of action is not definitively known, but CDP-choline may attenuate post-injury

functional deficits by several mechanisms, including providing the ACh precursor choline to drive up ACh synthesis, maintaining cell integrity by accelerating membrane formation, and/or stimulating brain metabolism. [122]

Clinical studies

Like with many immunonutrients, a number of large-scale studies have shown no benefit despite promising animal trials. Ruff et al. found that citicoline (an intermediate in the generation of phosphatidylcholine from choline) supplementation in TBI patients did not improve the extent or speed the recovery in patients following acute stroke. [123]

Similarly, Zafonte et al., completed the Citicoline Brain Injury Treatment Trial (COBRIT), a phase III, double-blind study comparing citicoline versus placebo. In this trial, 1213 study participants with complicated mild, moderate, or severe TBI were randomized to receive 2000 milligrams of citicoline or placebo daily for 90 days. The trial ran from 2007-2011 but was terminated early due to futility. The study did not demonstrate any benefits of citicoline treatment. [123]

Summary

Not all promising findings in the preclinical arena have been translated to success in patients. Choline supplementation in TBI rats holds promise. However, these have not held true in the patient models. This creates a need to understand the mechanism of how choline induces positive results in rats. Additionally, there may be other compounds or physiologic conditions that are necessary to allow for the beneficial effects of choline which are as of yet unknown.

11. Creatine

Creatine is a common dietary supplement, frequently used to increase strength and muscle mass. Creatine metabolism plays a key role in ATP turnover in the metabolically active brain. Endogenously expressed, cerebral creatine levels have been observed to decrease after TBI and recent studies have also shown that it provides significant neuroprotection against oxidative stress and ischemia. [124, 125] While investigations of creatine as a nutritional component of TBI therapy have been limited to animal models, much potential exists for clinical research to further define its translational relevance.

Biological pathways

The mechanisms of creatine-induced neuroprotection seem to be largely related to its effects on mitochondrial bioenergetics, binding to mitochondrial creatine kinase (CK) to exert structural protection allowing the enzyme to maintain its ability to inhibit free radical generation. [126, 127] Creatine supplementation lowers mitochondrial membrane potentials and reduces mitochondrial levels of reactive oxygen species (ROS) and calcium while maintaining the levels of adenosine triphosphate (ATP). [126] Physiologically, these effects result in inhibition of mitochondrial permeability and reduced neuronal loss. [126] Hybrid hydrophobic derivatives of creatine, creatinyl amino acids, have been synthesized with the aim to

establish better penetration across the blood-brain barrier. *In vivo* these compounds maintain both their neuroprotective abilities and chemical stability. [128]

Animal studies

In experimental mouse and rat TBI models, chronic supplementation of creatine has been shown to decrease the extent of cortical damage by as much as 36% and 50%, respectively. [126] Compared to rats receiving a control diet, rats fed a creatine-enriched diet have also shown decreased levels of neurochemical markers of TBI-induced acute cellular injury. [127, 129] Many of these protective effects were demonstrated to follow a dose-dependent manner and cumulatively provide promising preclinical data to steer pilot clinical studies. [129]

12. Magnesium

Magnesium is essential for maintenance of vital cellular functions, including glycolysis, sustaining membrane structure and function, protein synthesis and DNA replication. [130] Magnesium also plays an important role in central nervous system following injury. It is known that after TBI, the normal homeostatic mechanisms of magnesium are deranged, resulting in a rapid decline in magnesium levels in the brain. [131] This disruption of normal magnesium homeostasis has actually been shown to correlate with the severity of neurologically-mediated behavioral deficits following injury. [132] As such, it has been postulated that magnesium pharmacotherapy may aid in the treatment of various CNS injuries, including ischemia and cortical lesions, and has been found to be effective in some of these arenas. Because of the critical function of magnesium, it is also postulated that manipulation of dietary magnesium may have an impact on the recovery of function following TBI.

Biological pathways

Magnesium plays an important role in homeostatic regulation of key pathways involved in the delayed secondary phase of brain injury. [133] During normal physiological processes, magnesium is a noncompetitive inhibitor of the NMDA receptors, thereby regulating calcium influx. [134] Following acute brain injury, tissue magnesium is depleted, leading to loss of homeostatic control of the NMDA receptors. The ensuing massive influx of calcium leads to neuronal degeneration and cell death. [133]

Animal studies

Previous research has shown that dietary magnesium deficiency prior to injury worsens recovery of function and that systemic administration of magnesium pre- or post-injury significantly improves functional recovery. A number of studies in rats have shown that treatment with magnesium after brain injury did offer neuroprotection. [133, 135-137] Bareyre et al. showed that in addition to beneficial effects on behavioral outcomes, magnesium supplementation in brain-injured rats attenuated cortical histological damage. [138] Magnesium therapy administered up to 24 hours after injury in rats significantly improved motor outcome and behavioral parameters in rats with severe diffuse traumatic axonal brain injury.

[139] Additionally, magnesium supplementation was shown to reduce long-term motor and cognitive deficits after TBI in rats which may result in decreased post-traumatic stress and anxiety. [140]

Clinical studies

Disruption of magnesium homeostasis has been observed in human traumatic brain injury. Despite a number of preclinical studies showing beneficial effects of magnesium supplementation in TBI, mostly in rat models, clinical studies in TBI patients have failed to show a consistent clinical benefit. Temkin et al. showed that continuous infusions of magnesium for 5 days given to patients within 8 hours of moderate or severe TBI were not neuroprotective and may even have a negative effect in the treatment of significant head injury. [141] However, in another prospective clinical trial by Dhandapani et al., magnesium sulfate administered to TBI patients within 12 hours of their injuries produced decreased mortality and improved neurologic patient outcome. [142] There have been a number of studies looking at the role of magnesium supplementation in combination with other pharmacological agents or physiological interventions, such as hypothermia and hyperoxia, again with varied results in both preclinical and clinical trials. A recent meta-analysis of all randomized controlled trials comparing magnesium supplementation in patients following acute TBI shows no evidence to support the use of magnesium beyond standard physiologic replacement. [143]

Summary

The success of magnesium in attenuating the process of neurodegeneration in animal models of brain injury has been widely studied with promising results. Unfortunately, these preclinical successes have not consistently translated into success in humans. Magnesium supplementation in TBI patients has produced varied results, requiring further investigation into not only magnesium supplementation but the secondary parameters that may affect clinical outcome in TBI patients.

13. Vitamin D

Vitamin D hormone (VDH; 1, 25-dihydroxyvitamin D₃) is recognized as a neurosteroid with downstream implications in many different CNS signaling cascades. [144] VDH deficiency is associated with dysregulated neuronal physiology and has been demonstrated to both exacerbate TBI and reduce the efficacy of progesterone treatment for TBI. [145-147]. The relationship between VDH and TBI is perhaps most important in aging populations, within which the former is high in prevalence and the latter is rising in incidence. [148, 149]

Biological pathways

With regards to TBI, vitamin D generally acts in an anti-inflammatory manner, by regulating intracellular calcium levels (hence reducing the effects of glutamate excitotoxicity) and enhancing free radical scavenging. [144] Much TBI-related vitamin D research investigates it

as a combined therapy with progesterone. The two hormones are proposed to act in a synergistic and perhaps compensatory manner, each of them having their own anti-inflammatory and oxidative damage-reducing properties. [144] Together, VDH and progesterone stimulate neural growth in cultured neurons following *in vitro* glutamate excitotoxicity. [145, 147]

Animal studies

In rat cortical contusion injury (CCI) models of TBI, combined therapy consisting of VDH and progesterone resulted in reduced expression of inflammatory genes; protection against cell death and DNA damage; and significant improvement in post-traumatic behavior in VDH-deficient rats. [148, 149]

Clinical studies

Limited clinical trials have shown promising results for VDH and progesterone combination therapy, improving outcomes and decreasing mortality rates after TBI. [144] VDH has a high safety profile and is inexpensive and easily administered. [147] Continued investigations will be critical to further elucidate its specific mechanisms of actions, differences in combination therapy and monotherapy, and potential for use in a therapeutic or preventative manner.

14. Zinc and other trace elements

Trace elements are known to be important modulators of cell physiology and growth, contributing to many key processes such as wound healing and the immune response. [150] Among trace elements, zinc is specifically critical for tissue repair and essential for the function of many enzymes and gene expression. [151, 152] The majority of zinc ions in the brain are bound to proteins while the remaining are sequestered in presynaptic neuronal vesicles. [151] Although neurotoxic at high levels, zinc mediates synaptic transmission and plasticity, and clinical studies have shown that after TBI patients lose excess zinc in urine in proportion to injury severity and are at increased risk for developing zinc deficiency. [152, 153] Dietary zinc regulates intestinal zinc absorption and plays an important role in zinc homeostasis, thus making zinc promising as a possible nutritional adjunct to TBI therapy. [154]

Biological pathways

To a large degree, there is some debate with regards to whether zinc is neuroprotective or neurotoxic. [155] Many studies have demonstrated zinc accumulation after brain injury, associating it with neurodegeneration and deposited aggregates of ubiquitinated proteins and thus linking altered zinc homeostasis to impaired protein degradation. [153, 156-160] Though zinc chelators were able to block these TBI-induced histological changes, they did not lead to improved post-TBI outcomes in rats. [152, 153]

Contrarily, the neuroprotective effects of zinc are also established at the basic science and animal model levels. After mechanical repetitive strain injury (RSI), neuronal-like cells have been shown to develop a cellular zinc deficiency, and zinc deficiency itself has been linked to impaired neuronal stem cell proliferation and compromised cellular repair. [161, 162]

Animal studies

In animal models, zinc reduces the development of behavioral deficits after TBI. [153, 163] Specifically, in a rat controlled cortical impact (CCI) model, zinc supplementation reduced anxiety and cognitive impairments. [153, 161, 163] This supplementation did not lead to increased neuronal cell death. [161] Further evidence of its potential therapeutic benefit comes from the fact that zinc deficiency has been demonstrated to result in increased cell death and altered glial immune responses in several different rat and mouse TBI models. [151, 153, 164, 165]

Clinical studies

Limited preclinical studies show that, after an initial period of total parenteral nutrition, dietary zinc supplementation of 22 milligrams per day using zinc gluconate significantly increases visceral protein mass in post-TBI patients, is associated with improved Glasgow Coma Scores, as well as mortality decrease from 26% to 12%. [153] With the recommended upper limit of dietary zinc being 40 milligrams per day, further clinical studies will clearly define the optimal doses and time windows to improve post-TBI deficits and prevent neurotoxicity and undesired effects to other organs. [153, 166]

Other trace elements

While zinc has been the most thoroughly studied trace element in the contexts of TBI therapy, few studies have investigated the potential roles of others. While most of these elements still present the same concerns of toxicity versus protection, preliminary results seem promising for continued research. [154]

- As described above for zinc, copper deficiency has also been linked to increased neuronal apoptosis in a rat model of TBI. [165]
- To prevent deposition of free iron from heme degradation, administration of heme oxygenase (HO) inhibitors such as tin protoporphyrin or iron chelators have shown to reduce pathophysiologic and neuromotor changes in post-TBI models. [167, 168]
- As mentioned previously in this chapter, selenium, acting as an antioxidant, reduces reactive oxygen species (ROS)-mediated apoptosis of neural precursor cells both *in vitro* and in a mouse model of TBI. [103]

15. Conclusion

TBI represents a heterogeneous pathophysiological process that is clearly a challenge to manage. Multiple clinical studies of nutritional strategies have not defined a specific pathway that can serve as a sole, standalone target in TBI nutritional therapy. Multidimensional treatment plans, perhaps incorporating some of the described nutritional adjuvants, will thus merit more investigations from both the bench and the bedside to elucidate effective strategies to best treat TBI patients. Unfortunately, many strategies that are promising in the lab or in animal models have not borne fruit in clinical trials to date.

Author details

T.M. Ayodele Adesanya, Rachael C. Sullivan, Stanislaw P.A. Stawicki and David C. Evans

The Ohio State University, Department of Surgery, Columbus, Ohio, USA

References

- [1] Charrueau C, Belabed L, Besson V, Chaumeil JC, Cynober L, Moinard C. Metabolic response and nutritional support in traumatic brain injury: evidence for resistance to renutrition. *J Neurotrauma*. 2009;26(11):1911-20.
- [2] Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, Barbey AK, et al. Omega-3 Fatty acids as a putative treatment for traumatic brain injury. *J Neurotrauma*. 2013;30(11):897-906.
- [3] Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM. A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH. *J Am Coll Surg*. 1996;183(2):145-54.
- [4] McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN Journal of parenteral and enteral nutrition*. 2009;33(3):277-316. Epub 2009/04/29.
- [5] Härtl R, Gerber LM, Ni Q, Ghajar J. Effect of early nutrition on deaths due to severe traumatic brain injury. *J Neurosurg*. 2008;109(1):50-6.
- [6] Liu S, Levine SR, Winn HR. Targeting ischemic penumbra: part I - from pathophysiology to therapeutic strategy. *J Exp Stroke Transl Med*. 2010;3(1):47-55.
- [7] Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. 2004;364(9442):1321-8. Epub 2004/10/12.
- [8] Mayurasakorn K, Williams JJ, Ten VS, Deckelbaum RJ. Docosahexaenoic acid: brain accretion and roles in neuroprotection after brain hypoxia and ischemia. *Current opinion in clinical nutrition and metabolic care*. 2011;14(2):158-67. Epub 2010/12/24.
- [9] Wu A, Ying Z, Gomez-Pinilla F. Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury. *J Neurotrauma*. 2007;24(10):1587-95.

- [10] Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. *J Neurotrauma*. 2004;21(10):1457-67.
- [11] Shin SS, Dixon CE. Oral fish oil restores striatal dopamine release after traumatic brain injury. *Neurosci Lett*. 2011;496(3):168-71.
- [12] Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. *Neurosurgery*. 2011;68(2):474-81; discussion 81.
- [13] Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. *J Neurosurg*. 2011;114(1):77-84.
- [14] Bailes JE, Mills JD. Docosahexaenoic acid reduces traumatic axonal injury in a rodent head injury model. *J Neurotrauma*. 2010;27(9):1617-24.
- [15] Ying Z, Feng C, Agrawal R, Zhuang Y, Gomez-Pinilla F. Dietary omega-3 deficiency from gestation increases spinal cord vulnerability to traumatic brain injury-induced damage. *PLoS One*. 2012;7(12):e52998.
- [16] Lewis M, Ghassemi P, Hibbeln J. Therapeutic use of omega-3 fatty acids in severe head trauma. *Am J Emerg Med*. 2013;31(1):273.e5-8.
- [17] Matsuoka Y, Nishi D, Yonemoto N, Hamazaki K, Hamazaki T, Hashimoto K. Potential role of brain-derived neurotrophic factor in omega-3 Fatty Acid supplementation to prevent posttraumatic distress after accidental injury: an open-label pilot study. *Psychother Psychosom*. 2011;80(5):310-2.
- [18] Zhou M, Martindale RG. Immune-modulating enteral formulations: optimum components, appropriate patients, and controversial use of arginine in sepsis. *Current gastroenterology reports*. 2007;9(4):329-37.
- [19] Bays HE. Safety considerations with omega-3 fatty acid therapy. *The American journal of cardiology*. 2007;99(6a):35c-43c. Epub 2007/03/21.
- [20] Watson PD, Joy PS, Nkonde C, Hessen SE, Karalis DG. Comparison of bleeding complications with omega-3 fatty acids + aspirin + clopidogrel--versus--aspirin + clopidogrel in patients with cardiovascular disease. *The American journal of cardiology*. 2009;104(8):1052-4. Epub 2009/10/06.
- [21] Burgos M, Neary JT, González FA. P2Y2 nucleotide receptors inhibit trauma-induced death of astrocytic cells. *J Neurochem*. 2007;103(5):1785-800.
- [22] Bhalala OG, Srikanth M, Kessler JA. The emerging roles of microRNAs in CNS injuries. *Nat Rev Neurol*. 2013;9(6):328-39.

- [23] Bell MJ, Robertson CS, Kochanek PM, Goodman JC, Gopinath SP, Carcillo JA, et al. Interstitial brain adenosine and xanthine increase during jugular venous oxygen desaturations in humans after traumatic brain injury. *Crit Care Med*. 2001;29(2):399-404.
- [24] Kochanek PM, Clark RS, Obrist WD, Carcillo JA, Jackson EK, Mi Z, et al. The role of adenosine during the period of delayed cerebral swelling after severe traumatic brain injury in humans. *Acta Neurochir Suppl*. 1997;70:109-11.
- [25] Bell MJ, Kochanek PM, Carcillo JA, Mi Z, Schiding JK, Wisniewski SR, et al. Interstitial adenosine, inosine, and hypoxanthine are increased after experimental traumatic brain injury in the rat. *J Neurotrauma*. 1998;15(3):163-70.
- [26] Schubert P, Kreutzberg GW. Cerebral protection by adenosine. *Acta Neurochir Suppl (Wien)*. 1993;57:80-8.
- [27] Robertson CL, Bell MJ, Kochanek PM, Adelson PD, Ruppel RA, Carcillo JA, et al. Increased adenosine in cerebrospinal fluid after severe traumatic brain injury in infants and children: association with severity of injury and excitotoxicity. *Crit Care Med*. 2001;29(12):2287-93.
- [28] Mitchell HL, Frisella WA, Brooker RW, Yoon KW. Attenuation of traumatic cell death by an adenosine A1 agonist in rat hippocampal cells. *Neurosurgery*. 1995;36(5):1003-7; discussion 7-8.
- [29] Li W, Dai S, An J, Xiong R, Li P, Chen X, et al. Genetic inactivation of adenosine A2A receptors attenuates acute traumatic brain injury in the mouse cortical impact model. *Exp Neurol*. 2009;215(1):69-76.
- [30] Dai SS, Xiong RP, Yang N, Li W, Zhu PF, Zhou YG. (Different effects of adenosine A2A receptors in the models of traumatic brain injury and peripheral tissue injury). *Sheng Li Xue Bao*. 2008;60(2):254-8.
- [31] Dai SS, Zhou YG. Adenosine 2A receptor: a crucial neuromodulator with bidirectional effect in neuroinflammation and brain injury. *Rev Neurosci*. 2011;22(2):231-9.
- [32] Dai SS, Li W, An JH, Wang H, Yang N, Chen XY, et al. Adenosine A2A receptors in both bone marrow cells and non-bone marrow cells contribute to traumatic brain injury. *J Neurochem*. 2010;113(6):1536-44.
- [33] Choo AM, Miller WJ, Chen YC, Nibley P, Patel TP, Goletiani C, et al. Antagonism of purinergic signalling improves recovery from traumatic brain injury. *Brain*. 2013;136(Pt 1):65-80.
- [34] Shohami E, Kaufer D, Chen Y, Seidman S, Cohen O, Ginzberg D, et al. Antisense prevention of neuronal damages following head injury in mice. *J Mol Med (Berl)*. 2000;78(4):228-36.

- [35] Moinard C, Delpierre E, Loï C, Neveux N, Butel MJ, Cynober L, et al. An oligomeric diet limits the response to injury in traumatic brain-injured rats. *J Neurotrauma*. 2013;30(11):975-80.
- [36] Zhao J, Liu Q, Cui J, Hong J, Song Z. (Research on motor dysfunction and the role of CTP after traumatic brain injury in rats). *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2003;34(3):559-61.
- [37] Ghirnikar RS, Lee YL, Li JD, Eng LF. Chemokine inhibition in rat stab wound brain injury using antisense oligodeoxynucleotides. *Neurosci Lett*. 1998;247(1):21-4.
- [38] Sun FY, Faden AI. Pretreatment with antisense oligodeoxynucleotides directed against the NMDA-R1 receptor enhances survival and behavioral recovery following traumatic brain injury in rats. *Brain Res*. 1995;693(1-2):163-8.
- [39] Cherian L, Chacko G, Goodman C, Robertson CS. Neuroprotective effects of L-arginine administration after cortical impact injury in rats: dose response and time window. *J Pharmacol Exp Ther*. 2003;304(2):617-23.
- [40] Jeter CB, Hergenroeder GW, Ward NH, Moore AN, Dash PK. Human traumatic brain injury alters circulating L-arginine and its metabolite levels: possible link to cerebral blood flow, extracellular matrix remodeling, and energy status. *J Neurotrauma*. 2012;29(1):119-27.
- [41] Cherian L, Robertson CS. L-arginine and free radical scavengers increase cerebral blood flow and brain tissue nitric oxide concentrations after controlled cortical impact injury in rats. *J Neurotrauma*. 2003;20(1):77-85.
- [42] Louin G, Neveux N, Cynober L, Plotkine M, Marchand-Leroux C, Jafarian-Tehrani M. Plasma concentrations of arginine and related amino acids following traumatic brain injury: Proline as a promising biomarker of brain damage severity. *Nitric Oxide*. 2007;17(2):91-7.
- [43] Degeorge ML, Marlowe D, Werner E, Soderstrom KE, Stock M, Mueller A, et al. Combining glial cell line-derived neurotrophic factor gene delivery (AdGDNF) with L-arginine decreases contusion size but not behavioral deficits after traumatic brain injury. *Brain Res*. 2011;1403:45-56.
- [44] Cherian L, Hlatky R, Robertson CS. Comparison of tetrahydrobiopterin and L-arginine on cerebral blood flow after controlled cortical impact injury in rats. *J Neurotrauma*. 2004;21(9):1196-203.
- [45] Bitner BR, Brink DC, Mathew LC, Pautler RG, Robertson CS. Impact of arginase II on CBF in experimental cortical impact injury in mice using MRI. *J Cereb Blood Flow Metab*. 2010;30(6):1105-9.
- [46] Cherian L, Chacko G, Goodman JC, Robertson CS. Cerebral hemodynamic effects of phenylephrine and L-arginine after cortical impact injury. *Crit Care Med*. 1999;27(11):2512-7.

- [47] Mendez DR, Cherian L, Robertson CS. Laser Doppler flow and brain tissue PO₂ after cortical impact injury complicated by secondary ischemia in rats treated with arginine. *J Trauma*. 2004;57(2):244-50.
- [48] Liu H, Goodman JC, Robertson CS. The effects of L-arginine on cerebral hemodynamics after controlled cortical impact injury in the mouse. *J Neurotrauma*. 2002;19(3):327-34.
- [49] Avila MA, Sell SL, Kadoi Y, Prough DS, Hellmich HL, Velasco M, et al. L-Arginine decreases fluid-percussion injury-induced neuronal nitrotyrosine immunoreactivity in rats. *J Cereb Blood Flow Metab*. 2008;28(10):1733-41.
- [50] DeWitt DS, Smith TG, Deyo DJ, Miller KR, Uchida T, Prough DS. L-arginine and superoxide dismutase prevent or reverse cerebral hypoperfusion after fluid-percussion traumatic brain injury. *J Neurotrauma*. 1997;14(4):223-33.
- [51] Prough DS, Kramer GC, Uchida T, Stephenson RT, Hellmich HL, Dewitt DS. Effects of hypertonic arginine on cerebral blood flow and intracranial pressure after traumatic brain injury combined with hemorrhagic hypotension. *Shock*. 2006;26(3):290-5.
- [52] Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med*. 1995;23(3):436-49. Epub 1995/03/01.
- [53] Trabold R, Krieg S, Schöller K, Plesnila N. Role of vasopressin V(1a) and V2 receptors for the development of secondary brain damage after traumatic brain injury in mice. *J Neurotrauma*. 2008;25(12):1459-65.
- [54] Rauen K, Trabold R, Brem C, Terpolilli NA, Plesnila N. Arginine vasopressin V1a receptor deficient mice have reduced brain edema and secondary brain damage following traumatic brain injury. *J Neurotrauma*. 2013.
- [55] Szmydynger-Chodobska J, Fox LM, Lynch KM, Zink BJ, Chodobski A. Vasopressin amplifies the production of proinflammatory mediators in traumatic brain injury. *J Neurotrauma*. 2010;27(8):1449-61.
- [56] Yuan ZH, Zhu JY, Huang WD, Jiang JK, Lu YQ, Xu M, et al. Early change of plasma and cerebrospinal fluid arginine vasopressin in traumatic subarachnoid hemorrhage. *Chin J Traumatol*. 2010;13(1):42-5.
- [57] Kleindienst A, Brabant G, Morgenthaler NG, Dixit KC, Parsch H, Buchfelder M. Following brain trauma, copeptin, a stable peptide derived from the AVP precursor, does not reflect osmoregulation but correlates with injury severity. *Acta Neurochir Suppl*. 2010;106:221-4.
- [58] Xu M, Su W, Huang WD, Lu YQ, Xu QP, Chen ZJ. Effect of AVP on brain edema following traumatic brain injury. *Chin J Traumatol*. 2007;10(2):90-3.

- [59] Huang WD, Pan J, Xu M, Su W, Lu YQ, Chen ZJ, et al. Changes and effects of plasma arginine vasopressin in traumatic brain injury. *J Endocrinol Invest.* 2008;31(11):996-1000.
- [60] Huang WD, Yang YM, Wu SD. Changes of arginine vasopressin in elderly patients with acute traumatic cerebral injury. *Chin J Traumatol.* 2003;6(3):139-41.
- [61] Sanui M, King DR, Feinstein AJ, Varon AJ, Cohn SM, Proctor KG. Effects of arginine vasopressin during resuscitation from hemorrhagic hypotension after traumatic brain injury. *Crit Care Med.* 2006;34(2):433-8.
- [62] Mésenge C, Charriaut-Marlangue C, Verrecchia C, Allix M, Boulu RR, Plotkine M. Reduction of tyrosine nitration after N(omega)-nitro-L-arginine-methylester treatment of mice with traumatic brain injury. *Eur J Pharmacol.* 1998;353(1):53-7.
- [63] Wada K, Chatzipanteli K, Busto R, Dietrich WD. Effects of L-NAME and 7-NI on NOS catalytic activity and behavioral outcome after traumatic brain injury in the rat. *J Neurotrauma.* 1999;16(3):203-12.
- [64] Gahm C, Danilov A, Holmin S, Wiklund PN, Brundin L, Mathiesen T. Reduced neuronal injury after treatment with NG-nitro-L-arginine methyl ester (L-NAME) or 2-sulfo-phenyl-N-tert-butyl nitron (S-PBN) following experimental brain contusion. *Neurosurgery.* 2005;57(6):1272-81; discussion -81.
- [65] Chen G, Shi J, Qi M, Yin H, Hang C. Glutamine decreases intestinal nuclear factor kappa B activity and pro-inflammatory cytokine expression after traumatic brain injury in rats. *Inflamm Res.* 2008;57(2):57-64.
- [66] Feng D, Xu W, Chen G, Hang C, Gao H, Yin H. Influence of glutamine on intestinal inflammatory response, mucosa structure alterations and apoptosis following traumatic brain injury in rats. *J Int Med Res.* 2007;35(5):644-56.
- [67] Petersen SR, Jeevanandam M, Holaday NJ, Lubhan CL. Arterial-jugular vein free amino acid levels in patients with head injuries: important role of glutamine in cerebral nitrogen metabolism. *J Trauma.* 1996;41(4):687-94; discussion 94-5.
- [68] Platt SR. The role of glutamate in central nervous system health and disease--a review. *Vet J.* 2007;173(2):278-86.
- [69] Luo P, Fei F, Zhang L, Qu Y, Fei Z. The role of glutamate receptors in traumatic brain injury: implications for postsynaptic density in pathophysiology. *Brain Res Bull.* 2011;85(6):313-20.
- [70] Baethmann A, Maier-Hauff K, Schürer L, Lange M, Guggenbichler C, Vogt W, et al. Release of glutamate and of free fatty acids in vasogenic brain edema. *J Neurosurg.* 1989;70(4):578-91.

- [71] Globus MY, Alonso O, Dietrich WD, Busto R, Ginsberg MD. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem.* 1995;65(4):1704-11.
- [72] Yamamoto T, Rossi S, Stiefel M, Doppenberg E, Zauner A, Bullock R, et al. CSF and ECF glutamate concentrations in head injured patients. *Acta Neurochir Suppl.* 1999;75:17-9.
- [73] Rao VL, Başkaya MK, Doğan A, Rothstein JD, Dempsey RJ. Traumatic brain injury down-regulates glial glutamate transporter (GLT-1 and GLAST) proteins in rat brain. *J Neurochem.* 1998;70(5):2020-7.
- [74] Matsushita Y, Shima K, Nawashiro H, Wada K. Real-time monitoring of glutamate following fluid percussion brain injury with hypoxia in the rat. *J Neurotrauma.* 2000;17(2):143-53.
- [75] Matsushita Y, Shima K, Nawashiro H, Wada K, Tsuzuki N, Miyazawa T. Real time monitoring of glutamate following fluid percussion brain injury with hypoxia in the rat. *Acta Neurochir Suppl.* 2000;76:207-12.
- [76] Stover JF, Schöning B, Beyer TF, Woiciechowsky C, Unterberg AW. Temporal profile of cerebrospinal fluid glutamate, interleukin-6, and tumor necrosis factor-alpha in relation to brain edema and contusion following controlled cortical impact injury in rats. *Neurosci Lett.* 2000;288(1):25-8.
- [77] Ros J, Jones D, Pecinska N, Alessandri B, Boutelle M, Landolt H, et al. Glutamate infusion coupled with hypoxia has a neuroprotective effect in the rat. *J Neurosci Methods.* 2002;119(2):129-33.
- [78] van Landeghem FK, Stover JF, Bechmann I, Brück W, Unterberg A, Bührer C, et al. Early expression of glutamate transporter proteins in ramified microglia after controlled cortical impact injury in the rat. *Glia.* 2001;35(3):167-79.
- [79] Stover JF, Unterberg AW. Increased cerebrospinal fluid glutamate and taurine concentrations are associated with traumatic brain edema formation in rats. *Brain Res.* 2000;875(1-2):51-5.
- [80] Vespa P, Prins M, Ronne-Engstrom E, Caron M, Shalmon E, Hovda DA, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. *J Neurosurg.* 1998;89(6):971-82.
- [81] Palmer AM, Marion DW, Botscheller ML, Redd EE. Therapeutic hypothermia is cytoprotective without attenuating the traumatic brain injury-induced elevations in interstitial concentrations of aspartate and glutamate. *J Neurotrauma.* 1993;10(4):363-72.
- [82] van Landeghem FK, Weiss T, Oehmichen M, von Deimling A. Decreased expression of glutamate transporters in astrocytes after human traumatic brain injury. *J Neurotrauma.* 2006;23(10):1518-28.

- [83] Zlotnik A, Gurevich B, Tkachov S, Maoz I, Shapira Y, Teichberg VI. Brain neuroprotection by scavenging blood glutamate. *Exp Neurol*. 2007;203(1):213-20.
- [84] Cao R, Hasuo H, Ooba S, Akasu T, Zhang X. Facilitation of glutamatergic synaptic transmission in hippocampal CA1 area of rats with traumatic brain injury. *Neurosci Lett*. 2006;401(1-2):136-41.
- [85] Yi JH, Hazell AS. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. *Neurochem Int*. 2006;48(5):394-403.
- [86] Muir KW. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. *Curr Opin Pharmacol*. 2006;6(1):53-60.
- [87] Mukhin A, Fan L, Faden AI. Activation of metabotropic glutamate receptor subtype mGluR1 contributes to post-traumatic neuronal injury. *J Neurosci*. 1996;16(19):6012-20.
- [88] Yi JH, Herrero R, Chen G, Hazell AS. Glutamate transporter EAAT4 is increased in hippocampal astrocytes following lateral fluid-percussion injury in the rat. *Brain Res*. 2007;1154:200-5.
- [89] Hinzman JM, Thomas TC, Burmeister JJ, Quintero JE, Huettl P, Pomerleau F, et al. Diffuse brain injury elevates tonic glutamate levels and potassium-evoked glutamate release in discrete brain regions at two days post-injury: an enzyme-based microelectrode array study. *J Neurotrauma*. 2010;27(5):889-99.
- [90] Dai SS, Zhou YG, Li W, An JH, Li P, Yang N, et al. Local glutamate level dictates adenosine A2A receptor regulation of neuroinflammation and traumatic brain injury. *J Neurosci*. 2010;30(16):5802-10.
- [91] Chamoun R, Suki D, Gopinath SP, Goodman JC, Robertson C. Role of extracellular glutamate measured by cerebral microdialysis in severe traumatic brain injury. *J Neurosurg*. 2010;113(3):564-70.
- [92] Allen JW, Ivanova SA, Fan L, Espey MG, Basile AS, Faden AI. Group II metabotropic glutamate receptor activation attenuates traumatic neuronal injury and improves neurological recovery after traumatic brain injury. *J Pharmacol Exp Ther*. 1999;290(1):112-20.
- [93] Zlotnik A, Sinelnikov I, Gruenbaum BF, Gruenbaum SE, Dubilet M, Dubilet E, et al. Effect of glutamate and blood glutamate scavengers oxaloacetate and pyruvate on neurological outcome and pathohistology of the hippocampus after traumatic brain injury in rats. *Anesthesiology*. 2012;116(1):73-83.
- [94] Maxwell WL, Bullock R, Landholt H, Fujisawa H. Massive astrocytic swelling in response to extracellular glutamate--a possible mechanism for post-traumatic brain swelling? *Acta Neurochir Suppl (Wien)*. 1994;60:465-7.

- [95] Meldrum BS. The role of glutamate in epilepsy and other CNS disorders. *Neurology*. 1994;44(11 Suppl 8):S14-23.
- [96] Yang DL, Xu JF. Effect of dipeptide of glutamine and alanine on severe traumatic brain injury. *Chin J Traumatol*. 2007;10(3):145-9.
- [97] Tani H, Bandrowski AE, Parada I, Wynn M, Huguenard JR, Prince DA, et al. Modulation of epileptiform activity by glutamine and system A transport in a model of post-traumatic epilepsy. *Neurobiol Dis*. 2007;25(2):230-8.
- [98] Heyland DK, Dhaliwal R. Role of Glutamine Supplementation in Critical Illness Given the Results of the REDOXS Study. *JPEN Journal of parenteral and enteral nutrition*. 2013;37(4):442-3.
- [99] Slemmer JE, Shacka JJ, Sweeney MI, Weber JT. Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging. *Curr Med Chem*. 2008;15(4):404-14.
- [100] Hall ED, Yonkers PA, Andrus PK, Cox JW, Anderson DK. Biochemistry and pharmacology of lipid antioxidants in acute brain and spinal cord injury. *J Neurotrauma*. 1992;9 Suppl 2:S425-42.
- [101] Hall ED, Vaishnav RA, Mustafa AG. Antioxidant therapies for traumatic brain injury. *Neurotherapeutics*. 2010;7(1):51-61.
- [102] Ikeda K, Negishi H, Yamori Y. Antioxidant nutrients and hypoxia/ischemia brain injury in rodents. *Toxicology*. 2003;189(1-2):55-61.
- [103] Yeo JE, Kang SK. Selenium effectively inhibits ROS-mediated apoptotic neural precursor cell death in vitro and in vivo in traumatic brain injury. *Biochim Biophys Acta*. 2007;1772(11-12):1199-210.
- [104] Falcão de Arruda IS, de Aguiar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. *Clin Sci (Lond)*. 2004;106(3):287-92.
- [105] Polidori MC, Mecocci P, Frei B. Plasma vitamin C levels are decreased and correlated with brain damage in patients with intracranial hemorrhage or head trauma. *Stroke*. 2001;32(4):898-902.
- [106] Gilgun-Sherki Y, Rosenbaum Z, Melamed E, Offen D. Antioxidant therapy in acute central nervous system injury: current state. *Pharmacol Rev*. 2002;54(2):271-84.
- [107] Razmkon A, Sadidi A, Sherafat-Kazemzadeh E, Mehrafshan A, Jamali M, Malekpour B, et al. Administration of vitamin C and vitamin E in severe head injury: a randomized double-blind controlled trial. *Clin Neurosurg*. 2011;58:133-7.
- [108] Bullock MR, Lyeth BG, Muizelaar JP. Current status of neuroprotection trials for traumatic brain injury: lessons from animal models and clinical studies. *Neurosurgery*. 1999;45(2):207-17; discussion 17-20.

- [109] Marshall LF, Maas AI, Marshall SB, Bricolo A, Fearnside M, Iannotti F, et al. A multi-center trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg.* 1998;89(4):519-25.
- [110] Muizelaar JP, Marmarou A, Young HF, Choi SC, Wolf A, Schneider RL, et al. Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II trial. *J Neurosurg.* 1993;78(3):375-82.
- [111] Bains M, Hall ED. Antioxidant therapies in traumatic brain and spinal cord injury. *Biochim Biophys Acta.* 2012;1822(5):675-84.
- [112] Mustafa AG, Singh IN, Wang J, Carrico KM, Hall ED. Mitochondrial protection after traumatic brain injury by scavenging lipid peroxyl radicals. *J Neurochem.* 2010;114(1):271-80.
- [113] Jeter CB, Hergenroeder GW, Ward NH, Moore AN, Dash PK. Human mild traumatic brain injury decreases circulating branched-chain amino acids and their metabolite levels. *J Neurotrauma.* 2013;30(8):671-9.
- [114] Cole JT, Sweatt AJ, Hutson SM. Expression of mitochondrial branched-chain aminotransferase and α -keto-acid dehydrogenase in rat brain: implications for neurotransmitter metabolism. *Front Neuroanat.* 2012;6:18.
- [115] Cole JT, Mitala CM, Kundu S, Verma A, Elkind JA, Nissim I, et al. Dietary branched chain amino acids ameliorate injury-induced cognitive impairment. *Proc Natl Acad Sci U S A.* 2010;107(1):366-71.
- [116] Aquilani R, Iadarola P, Contardi A, Boselli M, Verri M, Pastoris O, et al. Branched-chain amino acids enhance the cognitive recovery of patients with severe traumatic brain injury. *Arch Phys Med Rehabil.* 2005;86(9):1729-35.
- [117] Aquilani R, Boselli M, Boschi F, Viglio S, Iadarola P, Dossena M, et al. Branched-chain amino acids may improve recovery from a vegetative or minimally conscious state in patients with traumatic brain injury: a pilot study. *Arch Phys Med Rehabil.* 2008;89(9):1642-7.
- [118] Vuille-Dit-Bille RN, Ha-Huy R, Stover JF. Changes in plasma phenylalanine, isoleucine, leucine, and valine are associated with significant changes in intracranial pressure and jugular venous oxygen saturation in patients with severe traumatic brain injury. *Amino Acids.* 2012;43(3):1287-96.
- [119] Guseva MV, Hopkins DM, Scheff SW, Pauly JR. Dietary choline supplementation improves behavioral, histological, and neurochemical outcomes in a rat model of traumatic brain injury. *J Neurotrauma.* 2008;25(8):975-83.
- [120] Blusztajn JK. Choline, a vital amine. *Science.* 1998;281(5378):794-5.

- [121] Caamano J, Gomez MJ, Franco A, Cacabelos R. Effects of CDP-choline on cognition and cerebral hemodynamics in patients with Alzheimer's disease. Methods and findings in experimental and clinical pharmacology. 1994;16(3):211-8. Epub 1994/04/01.
- [122] Dixon CE, Ma X, Marion DW. Effects of CDP-choline treatment on neurobehavioral deficits after TBI and on hippocampal and neocortical acetylcholine release. J Neurotrauma. 1997;14(3):161-9.
- [123] Ruff RL, Riechers RG. Effective treatment of traumatic brain injury: learning from experience. JAMA. 2012;308(19):2032-3.
- [124] Signoretti S, Di Pietro V, Vagnozzi R, Lazzarino G, Amorini AM, Belli A, et al. Transient alterations of creatine, creatine phosphate, N-acetylaspartate and high-energy phosphates after mild traumatic brain injury in the rat. Mol Cell Biochem. 2010;333(1-2):269-77.
- [125] Zhu S, Li M, Figueroa BE, Liu A, Stavrovskaya IG, Pasinelli P, et al. Prophylactic creatine administration mediates neuroprotection in cerebral ischemia in mice. J Neurosci. 2004;24(26):5909-12.
- [126] Sullivan PG, Geiger JD, Mattson MP, Scheff SW. Dietary supplement creatine protects against traumatic brain injury. Ann Neurol. 2000;48(5):723-9.
- [127] Saraiva AL, Ferreira AP, Silva LF, Hoffmann MS, Dutra FD, Furian AF, et al. Creatine reduces oxidative stress markers but does not protect against seizure susceptibility after severe traumatic brain injury. Brain Res Bull. 2012;87(2-3):180-6.
- [128] Burov S, Leko M, Dorosh M, Dobrodumov A, Veselkina O. Creatinyl amino acids: new hybrid compounds with neuroprotective activity. J Pept Sci. 2011;17(9):620-6.
- [129] Scheff SW, Dhillon HS. Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury. Neurochem Res. 2004;29(2):469-79.
- [130] Hoane MR, Gilbert DR, Barbre AB, Harrison SA. Magnesium dietary manipulation and recovery of function following controlled cortical damage in the rat. Magnes Res. 2008;21(1):29-37.
- [131] Vink R, McIntosh TK, Demediuk P, Faden AI. Decrease in total and free magnesium concentration following traumatic brain injury in rats. Biochem Biophys Res Commun. 1987;149(2):594-9.
- [132] Vink R, McIntosh TK. Pharmacological and physiological effects of magnesium on experimental traumatic brain injury. Magnes Res. 1990;3(3):163-9.
- [133] van den Heuvel C, Vink R. The role of magnesium in traumatic brain injury. Clin Calcium. 2004;14(8):9-14.
- [134] Garfinkel L, Garfinkel D. Magnesium regulation of the glycolytic pathway and the enzymes involved. Magnesium. 1985;4(2-3):60-72.

- [135] Feldman Z, Gurevitch B, Artru AA, Oppenheim A, Shohami E, Reichenthal E, et al. Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. *J Neurosurg.* 1996;85(1):131-7.
- [136] Hoane MR. Magnesium therapy and recovery of function in experimental models of brain injury and neurodegenerative disease. *Clin Calcium.* 2004;14(8):65-70.
- [137] Heath DL, Vink R. Optimization of magnesium therapy after severe diffuse axonal brain injury in rats. *J Pharmacol Exp Ther.* 1999;288(3):1311-6.
- [138] Bareyre FM, Saatman KE, Raghupathi R, McIntosh TK. Postinjury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. *J Neurotrauma.* 2000;17(11):1029-39.
- [139] Heath DL, Vink R. Improved motor outcome in response to magnesium therapy received up to 24 hours after traumatic diffuse axonal brain injury in rats. *J Neurosurg.* 1999;90(3):504-9.
- [140] Vink R, O'Connor CA, Nimmo AJ, Heath DL. Magnesium attenuates persistent functional deficits following diffuse traumatic brain injury in rats. *Neurosci Lett.* 2003;336(1):41-4.
- [141] Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. *Lancet Neurol.* 2007;6(1):29-38.
- [142] Dhandapani S, Gupta A, Vivekanandhan S, Sharma B, Mahapatra A. Randomized controlled trial of magnesium sulphate in severe closed traumatic brain injury. *The Indian Journal of Neurotrauma*; 2008. p. 27-33.
- [143] Arango MF, Bainbridge D. Magnesium for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2008(4):CD005400.
- [144] Aminmansour B, Nikbakht H, Ghorbani A, Rezvani M, Rahmani P, Torkashvand M, et al. Comparison of the administration of progesterone versus progesterone and vitamin D in improvement of outcomes in patients with traumatic brain injury: A randomized clinical trial with placebo group. *Adv Biomed Res.* 2012;1:58.
- [145] Atif F, Sayeed I, Ishrat T, Stein DG. Progesterone with vitamin D affords better neuroprotection against excitotoxicity in cultured cortical neurons than progesterone alone. *Mol Med.* 2009;15(9-10):328-36.
- [146] Cekic M, Cutler SM, VanLandingham JW, Stein DG. Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats. *Neurobiol Aging.* 2011;32(5):864-74.
- [147] Cekic M, Sayeed I, Stein DG. Combination treatment with progesterone and vitamin D hormone may be more effective than monotherapy for nervous system injury and disease. *Front Neuroendocrinol.* 2009;30(2):158-72.

- [148] Cekic M, Stein DG. Traumatic brain injury and aging: is a combination of progesterone and vitamin D hormone a simple solution to a complex problem? *Neurotherapeutics*. 2010;7(1):81-90.
- [149] Stein DG, Cekic MM. Progesterone and vitamin d hormone as a biologic treatment of traumatic brain injury in the aged. *PM R*. 2011;3(6 Suppl 1):S100-10.
- [150] Ekin S, Berber I, Kiymaz N. Effects of dexamethasone on trace elements and serum protein patterns following brain trauma in rats. *Biol Trace Elem Res*. 2005;107(1):53-60.
- [151] Doering P, Stoltenberg M, Penkowa M, Rungby J, Larsen A, Danscher G. Chemical blocking of zinc ions in CNS increases neuronal damage following traumatic brain injury (TBI) in mice. *PLoS One*. 2010;5(4):e10131.
- [152] Hellmich HL, Eidson K, Cowart J, Crookshanks J, Boone DK, Shah S, et al. Chelation of neurotoxic zinc levels does not improve neurobehavioral outcome after traumatic brain injury. *Neurosci Lett*. 2008;440(2):155-9.
- [153] Cope EC, Morris DR, Levenson CW. Improving treatments and outcomes: an emerging role for zinc in traumatic brain injury. *Nutr Rev*. 2012;70(7):410-3.
- [154] Levenson CW. Trace metal regulation of neuronal apoptosis: from genes to behavior. *Physiol Behav*. 2005;86(3):399-406.
- [155] Levenson CW. Zinc supplementation: neuroprotective or neurotoxic? *Nutr Rev*. 2005;63(4):122-5.
- [156] Hellmich HL, Eidson KA, Capra BA, Garcia JM, Boone DR, Hawkins BE, et al. Injured Fluoro-Jade-positive hippocampal neurons contain high levels of zinc after traumatic brain injury. *Brain Res*. 2007;1127(1):119-26.
- [157] Suh SW, Chen JW, Motamedi M, Bell B, Listiak K, Pons NF, et al. Evidence that synaptically-released zinc contributes to neuronal injury after traumatic brain injury. *Brain Res*. 2000;852(2):268-73.
- [158] Suh SW, Frederickson CJ, Danscher G. Neurotoxic zinc translocation into hippocampal neurons is inhibited by hypothermia and is aggravated by hyperthermia after traumatic brain injury in rats. *J Cereb Blood Flow Metab*. 2006;26(2):161-9.
- [159] Sun KJ, Zhu L, Wang HD, Ji XJ, Pan H, Chen M, et al. Zinc as mediator of ubiquitin conjugation following traumatic brain injury. *Brain Res*. 2013;1506:132-41.
- [160] Zhu L, Wang HD, Yu XG, Jin W, Qiao L, Lu TJ, et al. Erythropoietin prevents zinc accumulation and neuronal death after traumatic brain injury in rat hippocampus: in vitro and in vivo studies. *Brain Res*. 2009;1289:96-105.
- [161] Cope EC, Morris DR, Scrimgeour AG, Levenson CW. Use of zinc as a treatment for traumatic brain injury in the rat: effects on cognitive and behavioral outcomes. *Neurorehabil Neural Repair*. 2012;26(7):907-13.

- [162] Li Y, Hawkins BE, DeWitt DS, Prough DS, Maret W. The relationship between transient zinc ion fluctuations and redox signaling in the pathways of secondary cellular injury: relevance to traumatic brain injury. *Brain Res.* 2010;1330:131-41.
- [163] Cope EC, Morris DR, Scrimgeour AG, VanLandingham JW, Levenson CW. Zinc supplementation provides behavioral resiliency in a rat model of traumatic brain injury. *Physiol Behav.* 2011;104(5):942-7.
- [164] Yeiser EC, Vanlandingham JW, Levenson CW. Moderate zinc deficiency increases cell death after brain injury in the rat. *Nutr Neurosci.* 2002;5(5):345-52.
- [165] Penkowa M, Giralt M, Thomsen PS, Carrasco J, Hidalgo J. Zinc or copper deficiency-induced impaired inflammatory response to brain trauma may be caused by the concomitant metallothionein changes. *J Neurotrauma.* 2001;18(4):447-63.
- [166] Zhu L, Yan W, Qi M, Hu ZL, Lu TJ, Chen M, et al. Alterations of pulmonary zinc homeostasis and cytokine production following traumatic brain injury in rats. *Ann Clin Lab Sci.* 2007;37(4):356-61.
- [167] Potts MB, Koh SE, Whetstone WD, Walker BA, Yoneyama T, Claus CP, et al. Traumatic injury to the immature brain: inflammation, oxidative injury, and iron-mediated damage as potential therapeutic targets. *NeuroRx.* 2006;3(2):143-53.
- [168] Chang EF, Claus CP, Vreman HJ, Wong RJ, Noble-Haeusslein LJ. Heme regulation in traumatic brain injury: relevance to the adult and developing brain. *J Cereb Blood Flow Metab.* 2005;25(11):1401-17.